



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/581,861 | 03/05/2001 | James R. Broach | 60623CIP(50370) | 4402 |

21874 7590 07/08/2005

EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

| |
|----------|
| EXAMINER |
|----------|

CELSA, BENNETT M

| | |
|----------|--------------|
| ART UNIT | PAPER NUMBER |
|----------|--------------|

1639

DATE MAILED: 07/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/581,861

Applicant(s)

BROACH ET AL.

Examiner

Bennett Celsa

Art Unit

1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 April 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,5-43,45-50,52-55,57-61 and 109-119 is/are pending in the application.
- 4a) Of the above claim(s) 5-43,45-50,52,55,58,61 and 109-119 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 53, 54, 57, 59 and 60 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's amendment dated 4/19/05 is acknowledged.

Additionally, applicant's request for an interview is noted. Applicant may wish to contact the examiner to schedule a telephonic/personal interview in response to this office action.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 1, 5-43, 45-50, 52-55, 57-61 and 109-119 are presently pending.

Claims 1, 53, 54, 57, 59 and 60 are under consideration.

Claims 5-43, 45-50, 52, 55, 58, 61 and 109-119 are withdrawn from consideration as being directed to a nonelected invention.

Election/Restrictions

Applicant's election with traverse of Group 3 (claims 1 and 2 (in part); 3 and 44-61) drawn to: recombinant yeast comprising heterologous GPCR and chimera of GPA1 (≥ 4 c-terminal substituted with heterologous G protein subunit amino acids) and optionally linked to at least the 1st five amino acids of a 2nd heterologous G protein subunit in the reply filed on 8/20/04 was previously acknowledged.

Applicant's further election of the "*single disclosed species*" of the human bradykinin receptor as the heterologous G protein coupled receptor and the sandwich chimera Galphaq(1-11)-GPA1 (6-467)-Galpaq(355-359) of Example 12, which

Art Unit: 1639

substitutes both the N and C terminus of GPA1 with 1st and 2nd heterologous subunits derived from the same source, in the reply filed on 8/20/04 was previously acknowledged.

The above requirement was previously made FINAL.

2. This application contains claims 5-43, 45-50, 52, 55, 58, 61 and 109-119 drawn to a nonelected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The present application (09/581,861 filed 3/5/2001) claims priority under:

- a. 371 of PCT/US98/21168 (filed 10/07/98); and
- b. CIP of 08/946,298 (filed 10/7/97) as well as earlier applications.

Art Unit: 1639

Upon review of the two above cited documents, the presently claimed (and elected invention) finds disclosure support in the PCT/US98/21168 application (filed 10/07/98) BUT not the 08/946,298 (filed 10/7/97) application which lacks direct or exemplary support for the presently claimed scope of claims e.g. the substitution GPA variants as well as the sandwich chimeras. Accordingly, the present elected claims are granted the filing date of the PCT application (e.g. 10/7/98) for purposes of prior art.

Withdrawn Objection (s) and/or Rejection (s)

Applicant's amendment and accompanying arguments have overcome the following prior art rejections:

- i. Claims 1-2, 44 and 56, are rejected under 35 U.S.C. 102(a,b,e) as being anticipated by Pausch et al. WO 95/21925 (8/95).
- ii. Claims 1-2, 44 and 56, are rejected under 35 U.S.C. 102(a,b,e) as being anticipated by Fowlkes et al. WO 94/23025(10/94: filed 3/94 or earlier).
- iii. Claims 1-2, 44, 56 and 57 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Brown et al. WO 99/14344.
- iv. Claims 1-2, 44, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al. and Conklin et al. Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890.
- v. Claims 1-2, 44, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fowlkes et al. WO 94/23025(10/94: filed 3/94 or earlier).

Art Unit: 1639

vi. Claims 1-2, 44, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. WO 99/14344 and Conklin et al. Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890.

Outstanding Objection (s) and/or Rejection (s)

Claims 1, 53, 54, 57, 59 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al. WO 95/21925 (8/95), Fowlkes et al. WO 94/23025(10/94: filed 3/94 or earlier), Brown et al. WO 99/14344, and/or Conklin et al. Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890 in view of Hamm, J. Biol. Chem. Vol. 273(2) (Jan. 1998) pages 669-672.

The teaching of the Pausch et al., Fowlkes et al. and Brown et al. references taken separately or in combination with the Conklin reference, as discussed in the following rejections presented in the 10/19/04 first office action, is hereby incorporated by reference in their entirety:

- i. Claims 1-2, 44 and 56, are rejected under 35 U.S.C. 102(a,b,e) as being anticipated by Pausch et al. WO 95/21925 (8/95).
- ii. Claims 1-2, 44 and 56, are rejected under 35 U.S.C. 102(a,b,e) as being anticipated by Fowlkes et al. WO 94/23025(10/94: filed 3/94 or earlier).
- iii. Claims 1-2, 44, 56 and 57 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Brown et al. WO 99/14344.

Art Unit: 1639

iv. Claims 1-2, 44, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al. and Conklin et al. Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890.

v. Claims 1-2, 44, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fowlkes et al. WO 94/23025(10/94: filed 3/94 or earlier).

vi. Claims 1-2, 44, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. WO 99/14344 and Conklin et al. Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890.

As discussed in the above cited i-vi. prior art rejections of record, the above cited references teach recombinant yeast cells comprising heterologous G-protein coupled receptor (GPCR) which act as a "surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell ; and "chimeric G-Protein subunits" such that expression of the chimeric G-protein subunit comprising a GPA1 subunit C-terminally substituted with at least the last four C-terminal amino acids of a heterologous G alpha protein subunit functionally integrates said heterologous GPCR into the pheromone response pathway of the yeast cell, wherein modulation of the signal transduction activity of said heterologous GPCR by an extracellular signal provides a detectable signal.

The above reference teaching(s) of a chimeric Galpha protein subunit differs from the presently claimed invention (e.g. claims 1, 53, 54, 57, 59 and 60) by failing to additionally modify the N-terminus portion of GPA1 to operably link/substitute "at least

Art Unit: 1639

the first five N-terminal amino acids" (e.g. the 1st 11 N-terminal amino acids: see claims 54 and 60) of a 2nd heterologous G protein subunit.

The Hamm reference teaches the structure and role of the G protein heterotrimer; particularly the different G α subunits and their corresponding receptors (e.g. including bradykinin: see page 669; page 670, right column). The Hamm reference teaches that in addition to the C-terminus of G protein α subunits being critical in determining receptor-G protein specificity (as discussed in the above Pausch, Fowlkes, Brown and Conklin references), the N-terminus of the α G-protein subunit also appears to be involved in promoting heterologous receptor contact or coupling. E.g. see Abstract; page 669, especially right column; the figures, especially figures 1 and 2, but particularly figure 2 and the role of the 1st N-terminal 23 amino acids of G α and rhodopsin receptor)

Accordingly, the Hamm reference would provide motivation to one of ordinary skill in the art at the time of applicant's invention to further modify the chimeric G α protein subunits obtained by the Pausch, Fowlkes, Brown and Conklin references by linking or substituting into the N terminal portion of the reference chimeras corresponding heterologous amino acids in order to obtain sandwich chimeras (e.g. N-term heterologous-GPA1-C terminal heterologous) that can be screened for different degrees (e.g. increased/decreased) of heterologous receptor coupling.

The determination of the optimum number of N-terminally linked or substituted heterologous amino acids (e.g. at least 5 ; i.e. 11) with regard to a particular heterologous receptor and corresponding chimera construct was well within the skill of

Art Unit: 1639

the art utilized art-recognized screening techniques. E.g. see Pausch, Fowlkes, Brown and Conklin references and assays disclosed therein.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to additionally modify the N-terminus portion of GPA1 of the Pausch, Fowlkes, Brown and Conklin references chimeras to operably link "at least the first five N-terminal amino acids (e.g. the 1st 11 N-terminal amino acids: see claims 54 and 60) of a heterologous G protein subunit and arrive at the presently claimed sandwich chimeras with a reasonable expectation of success of obtaining modified chimeras which possessed varying degrees (e.g. increased/decreased) of heterologous receptor coupling for use in screening assays (e.g. receptor agonists/antagonists).

Discussion

Applicant's arguments directed to the above obviousness rejection were considered but deemed nonpersuasive for the following reasons.

Applicant argues that the Hamm reference does not teach that the N-terminus of G protein alpha subunits is critical to promoting heterologous receptor contact or coupling.

The Examiner respectfully disagrees.

As discussed in the rejection above, the Hamm reference specifically teaches that the N-terminal regions of the alpha subunit along with the C-terminal region of the gamma subunit are both sites of lipid modification suggesting *a site of membrane attachment* (e.g. emphasis provided: see Hamm p. 669, right column 2nd full paragraph). Additionally evidence provided by references cited by Hamm leads to the conclusion by

Art Unit: 1639

the Hamm reference that "A larger region of the C-terminal region of the Galpha subunits, as well as the N-terminal helix, has been *implicated in receptor contact*" (emphasis provided: See Hamm p. 669, right column, penultimate paragraph).

Accordingly, in contradistinction to applicant's argument, the Hamm reference does specifically teach and/or suggest that the N-terminus of G protein alpha subunits is critical to promoting heterologous receptor contact or coupling.

Applicant further argues that "there is no teaching in the Hamm reference (or any of the other references), as to which amino acids in the N-terminus should be linked or substituted.

The Examiner respectfully disagrees.

Initially, it is noted that the claimed invention broadly encompasses the linking to or replacing *at least the first five amino acids* of the N-terminus of GPA1; but would encompass the entire N-terminus.

Additionally, as pointed out in the rejection above, the Hamm reference teaches and/or suggests that the N-terminus of the alpha G-protein alpha subunit is involved in promoting heterologous receptor contact or coupling. E.g. see Abstract; page 669, especially right column; the figures, especially figures 1 and 2. More particularly the reference points to the role of the 1st N-terminal 23 amino acids of the G-protein alpha subunit. See e.g. figure 1, but particularly figure 2 and the role of the 1st N-terminal 23 amino acids of Galpha and rhodopsin receptor.

Accordingly, applicant's claims broadly encompass operably linking and/or substituting 5 or more (e.g. the entire N-terminus) amino acids of the N-terminus. In this

Art Unit: 1639

respect, the reference provides guidance as to linking and/or substituting of 1 or more N-terminal amino acids up to the 23rd amino acid.

Applicant further argues that the Hamm reference teaching that the N-terminus of alpha G-protein subunit **appears** (applicant emphasis) to be involved in promoting heterologous receptor contact or coupling merely is teaching that modifying the N-terminus would be "obvious to try" and would not engender a "reasonable expectation of success".

This argument was considered but deemed nonpersuasive for the following reasons.

The Examiner is not applying an improper "obvious to try" rationale in support of an obviousness rejection. Regarding 'obvious to try':

"The admonition that obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." See *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (citations omitted)

In contradistinction to applicant' s argument, the Hamm reference provides a clear suggestion and guidance as to how and where to modify the prior art chimeric proteins to produce the claimed invention along with evidence suggesting the modification would be successful; and further enabling methodology (recombination;mutagenesis etc.) to achieve such modification is known in the art and

Art Unit: 1639

further discussed in the primary references. Accordingly, the above obviousness rejection does not employ an improper 'obvious to try' rationale.

Additionally, it is noted that reasonable expectation of success and not absolute certainty is the standard for obviousness.

In the present instance although the Hamm reference admits that the C-terminus of the alpha subunit is the best characterized receptor contact region, the reference nevertheless provides evidence (as discussed above) that implicates the N-terminus in receptor contact and membrane attachment. Accordingly, the Hamm reference provides motivation to one of ordinary skill in the art to modify the N-terminus of alpha G-protein subunit in a manner analogous to that performed on the C-terminus in accordance with the the Pausch et al., Fowlkes et al. and Brown et al., Conklin ferences with a reasonable expectation of making a yeast cell comprising a chimeric G-protein subunit and heterologous G-protein-coupled receptor which act as a "surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell .

Accordingly, the above obviousness rejection is hereby maintained.

Art Unit: 1639

Conclusion

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

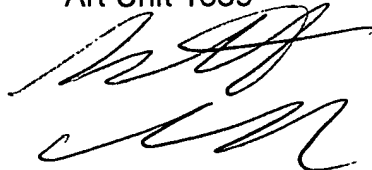
Future Correspondence:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639



BC
July 1, 2005